EXHIBIT A

**Heart Failure Society of America (HFSA)
Practice Guidelines**

Heart Failure Society of America (HFSA) Practice Guidelines

HFSA Guidelines for Management of Patients With Heart Failure Caused by Left Ventricular Systolic Dysfunction—Pharmacological Approaches

HEART FAILURE SOCIETY OF AMERICA

Minneapolis, Minnesota

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HEART FAILURE SOCIETY GUIDELINES: A MODEL
OF CONSENSUS AND EXCELLENCE

The first guidelines prepared by the Guideline Committee for the Heart Failure Society of America appear in this issue of the *Journal of Cardiac Failure*. The publication of these guidelines is a seminal event in the growth of the Heart Failure Society because it represents our first effort to provide didactic education for physicians and other health professionals outside of the context of the Annual Scientific Meeting. Because of the importance of these guidelines for both the Society and the practicing physician, it is important to describe the process by which these guidelines were developed and approved by the Society before their publication.

The Guideline Committee was established as a standing committee by the Executive Council, and the membership and Chairperson of the committee were selected by the Nominating Committee of the Society with the approval of the Executive Council. Care was taken in selecting the initial committee to insure that its membership represented different geographic regions, diverse expertise, and varying therapeutic philosophies. This group was then charged with developing not only a guideline but also a procedural paradigm that would provide a platform for the development of future guidelines.

During the development of the guidelines, the committee had several face-to-face meetings; however, a substantial portion of the work was accomplished through the assiduous use of teleconferencing. The cost of these meetings was supported exclusively by the Society. A draft representing the committee's consensus opinion was completed in May 1999 and submitted to the Executive Council for approval. The members of the Executive Council had the opportunity to provide written comments, and areas of concern were adjudicated by teleconference between the committee and members of the Executive Council. The Council then met to discuss the guidelines in September 1999, at which time the major recommendations were unanimously approved. Subsequently, the major recommendations were presented to the membership of the Society during the Annual Scientific Meeting. The Society membership provided important insights, many of which were then incorporated into the final document. Finally, after submission of final comments, the complete text of the guidelines document was approved by the Executive Council and the Guideline Committee during a telephone conference held in October 1999. Thus, the guidelines underwent a scrupulous review process with both comments and consensus being obtained from a large group of stakeholders. However, this document could not have come to fruition without the superb efforts of the Chair and membership of the Guideline Committee.

With the publication of these guidelines, we now face new challenges. First, it is incumbent upon the Society to develop methods to disseminate the guidelines to the practitioner. Second, it will be important to insure that the guidelines can be updated in a timely manner so they become a living document. Finally, the Guideline Committee will be challenged to address other issues in heart failure management. However, the process developed for this outstanding work has clearly provided a paradigm for future efforts.

Arthur M. Feldman, M.D., Ph.D.
President, HFSA

Heart failure is one of the major public health problems facing the United States today. Furthermore, demographic and clinical evidence strongly suggests that the prevalence of heart failure will increase substantially in the next decade, which will enhance the adverse public health impact of this syndrome. The Heart Failure Society of America is dedicated to the development of strategies to deal more effectively with the many epidemiological, clinical, research, and therapeutic issues that surround this syndrome. The Guideline and Clinical Positions Committee of the Heart Failure Society of America has the charge to review ongoing clinical research and expert opinion and to develop and maintain a dynamic synthesis of this information as a state-of-the-art clinical practice guideline. All documents that come from our committee are produced without commercial support and have been reviewed and approved by the Executive Council of the Heart Failure Society.

The rapid pace of therapeutic developments and the major public health impact of certain diseases or syndromes have led to the proposal of various clinical practice guidelines to assist clinicians in the management of these disorders. Guidelines allow for the development of a rigorous, evidence-based approach using the outcome of clinical trials and the consensus of expert opinion. Heart failure presents an excellent opportunity for the application of clinical practice guideline methodology. The knowledge base concerning the optimal management of this syndrome continues to expand at a rapid pace. Practice guidelines are needed for the efficient translation of research advances into the care of patients with heart failure.

The present document represents the initial effort of our committee. The primary goal was to address areas in which significant developments have occurred since the publication of previous guidelines for heart failure care. The committee has limited its present focus to the pharmacological therapy of patients with heart failure caused by left ventricular systolic dysfunction. Our recommendations are based on the synthesis of many sources of evidence by a panel of experts in heart failure management. We have followed the general strategy used in the preparation of other clinical practice guidelines, particularly, that by the Agency for Health Care Policy and Research (AHCPR). Emphasis is placed on the results of well-designed and adequately controlled clinical trials performed in relevant patient populations (Strength of Evidence = A) and other useful investigations, including cohort studies (Strength of Evidence = B). In certain instances, expert opinion is the basis for a recommendation (Strength of Evidence = C). Our recommendations are presented as applicable without regard to race or gender. However, we acknowledge that currently available clinical trial data do not provide completely adequate information in this regard. Commitment to recruit women and minorities in future heart failure trials should improve our knowledge of the influence of race and gender on the pharmacological treatment of heart failure.

This document represents the first in a series of reports by the Guideline and Clinical Positions Committee of the Heart Failure Society of America. Future plans include development of a comprehensive diagnostic and management guideline for heart failure and the implementation of a process for ongoing guideline revision based on new data. Heart failure management is undergoing rapid evolution on many fronts as scientists and clinicians better understand the pathophysiology of this condition and the effects of new drugs and devices. Systematic, ongoing effort will be required to bring new clinical advances into common practice for the ultimate benefit of patients with this disabling and life-threatening syndrome.

Brief Overview of Heart Failure

Public Health Implications

Heart failure is a varied clinical syndrome with a complex pathophysiology that is still being defined. These features have led to demanding therapeutic regimens that have made optimal management of heart failure a difficult enterprise. In addition, heart failure is common, and its public health consequences are ever growing. An estimated 4.8 million individuals are afflicted with this syndrome in the United States today, and 400,000 to 700,000 new cases are estimated to develop each year (1). The prevalence of heart failure increases with age; it approaches 10% of Americans in the ninth decade of life (2). Aging of the population and the prolonged survival of patients with a variety of cardiovascular diseases that culminate in ventricular dysfunction ensure that the magnitude of the heart failure problem will substantially worsen in the next decade. Experts have projected a 2- to 3-fold increase in prevalence (3). In addition to being a common condition, heart failure causes substantial morbidity with total hospitalizations, directly and indirectly related, exceeding 3 million per year. This condition directly or indirectly contributes to the death of approximately 250,000 individuals a year (4–7). Advanced heart failure remains one of the most disabling and lethal medical conditions (8). Readmission shortly after hospital discharge remains disturbingly common, and most patients continue to experience limiting symptoms and often poor quality of life despite treatment. The economic burden of the syndrome is staggering, with estimated direct medical expenditures in excess of $20 billion per year (4,9).

Definition and Pathophysiology

Heart failure remains the final common pathway for many cardiovascular diseases whose natural history results in symptomatic or asymptomatic left ventricular dysfunction. Although left ventricular diastolic dysfunction is an important part of the clinical spectrum of heart failure, our review will be restricted to patients with left ventricular systolic dysfunction. This condition is accompanied by a number of pathophysiological abnormalities (10), including structural remodeling and dilation of the left ventricular chamber; reduced myocyte shortening and wall motion; sodium retention and circulatory congestion; systemic vasoconstriction and vascular remodeling that increases impedance of left ventricular ejection (11); and neurohormonal activation that contributes to many of the above pathophysiological events (12,13).

A number of basic and clinical investigations have highlighted the major importance of the renin-angiotensin-aldosterone system (RAAS) in the generation and progression of heart failure. The traditional pharmacological means of blocking the activity of the RAAS has been through the inhibition of angiotensin-converting enzyme (ACE), which limits the production of angiotensin II, the major active biological peptide of this system. ACE inhibitors initially were viewed as "vasodilator" therapy because of their ability to reverse smooth muscle vasoconstriction in peripheral arterioles and, thus, substantially lower the elevated systemic vascular resistance that contributes to hemodynamic decompensation in heart failure. It is now clear, however, that the long-term benefits of ACE inhibitors and other newer therapies are dependent to a large extent on their ability to cause regression of some of the structural abnormalities and not on their hemodynamic effects. Progression of heart failure is the hallmark of patients with left ventricular dysfunction. Dysfunction appears to beget additional dysfunction in a downward spiral that culminates in the demise of the patient. An improved understanding of the factors that promote progressive cardiac dysfunction focused attention on the ability of various neurohormones to cause progressive remodeling or structural alteration of the heart in the form of dilatation and hypertrophy (14,15). Substantial clinical and basic evidence now links this remodeling process to the development of progressive ventricular dysfunction that is commonly seen in heart failure. Recognition of cardiac remodeling as a key component of the progressive heart failure syndrome highlights not only the RAAS but also the important role of the kinin system, as well as the excess sympathetic activity that is commonly present in heart failure (16). In addition, a number of other hormonal systems appear to contribute to adverse myocardial remodeling. Endothelin-1 and various cytokines, including tumor necrosis factor (TNF)-α, are often activated in severe heart failure and have recently become new targets for drug development. Evidence for the involvement of multiple neurohormonal systems supports the concept that the pathophysiology of heart failure is intimately linked to diffuse activation of these systems. The adverse role of coronary artery disease in the process of cardiac remodeling has received attention as well (17). The therapeutic implications of cardiac remodeling are evident in the approach taken in this guideline.

Current Therapy and New Guidelines

Current therapeutic approaches stress the role of ACE inhibitors, diuretics, and digoxin. Therapeutic strategies to counteract neurohormonal activation have traditionally focused on inhibition of the renin-angiotensin sys-

tem through the blockade of ACE, a key catalytic protein in the generation of angiotensin II and the breakdown of bradykinin. Definitive evidence for the use of ACE inhibitors to limit the morbidity and mortality of heart failure patients has been established through numerous clinical trials and investigations. The reader is urged to review this impressive array of evidence that is detailed in previous guidelines (18–21).

A comprehensive algorithm for the treatment of left ventricular systolic dysfunction is beyond the scope of the present work. The guideline that we are proposing acknowledges the important role of digoxin and diuretics and the essential role of ACE inhibitors in the treatment of left ventricular systolic dysfunction. We endorse the general framework for the use of these agents as expressed in previous heart failure guidelines. The availability of new data on digoxin caused us to include this agent in our present guideline recommendations. A brief review of the essential aspects of ACE inhibitors and diuretic therapy is presented here as background for the remainder of our specific guideline recommendations.

ACE inhibitors remain pivotal agents for the treatment of left ventricular systolic dysfunction. These drugs provide symptomatic relief and favorably affect the risk of morbidity and mortality in patients with symptomatic heart failure as established in the SOLVD (for the complete name of this and other clinical trials, see Appendix B) Treatment Trial. In addition, the SOLVD Prevention Trial convincingly showed the value of ACE inhibition in patients with severe asymptomatic left ventricular systolic dysfunction. The risk of developing heart failure and the likelihood of hospitalization for heart failure were significantly reduced by treatment with enalapril. The favorable effects of ACE inhibition on mortality in patients with advanced heart failure (New York Heart Association [NYHA] class IV) were also shown in the CONSENSUS Study. Results from randomized, double-blind, controlled trials consequently provided definitive evidence for the systematic use of ACE inhibitors in patients with left ventricular systolic dysfunction. Available data suggest that the beneficial effects of ACE inhibitors in heart failure are a class effect.

There are some contraindications to the use of ACE inhibitors in patients with heart failure, but the great majority can be successfully treated with these agents. The concept of low initial doses with adjustment of diuretic dose as needed to avoid hypotension and deterioration in renal function remains valid. Up-titration to the target doses used in clinical trials is generally recommended.

Congestion remains an important complication in many patients with heart failure. Although ACE inhibition may diminish evidence of congestion, diuretic agents are usually needed for adequate control of volume status. Thiazides may be effective in some patients with

evidence of mild fluid overload and normal renal function, but most congested patients with systolic dysfunction require loop diuretics. Patients with advanced heart failure and compromised renal function often require multiple diuretics with different sites of renal action. The value of sodium restriction for the chronic treatment of volume overload cannot be overemphasized and, often in conjunction with ACE inhibition, it helps reduce the need for diuretic. After initial relief of congestion and up-titration of ACE inhibition, significant dietary sodium restriction may allow for discontinuation of diuretics in some patients. Side effects, particularly metabolic abnormalities and electrolyte derangements, remain common with diuretic therapy. Potassium depletion is particularly troublesome, and replacement therapy is frequently necessary to maintain serum potassium levels of greater or equal to 4.0 mmol/L, even though this is less commonly seen in ACE inhibitor–treated patients.

The present guideline assumes that these fundamental aspects that concern ACE-inhibitor and diuretic therapy remain essential for optimal care of heart failure patients. Our guideline builds on this framework by focusing on the evolution of specific pharmacological treatments for heart failure that are additive to the benefits obtained for ACE inhibitors and diuretics. We concentrated on areas in which significant new data have recently appeared that require new consensus recommendations. We have specifically chosen to comment on the use of β-adrenergic receptor blockers, digoxin, antiplatelet and anticoagulation therapy, angiotensin receptor blockers, amiodarone, spironolactone, and therapy for myocarditis.

Recommendations for Pharmacological Therapy: Left Ventricular Systolic Dysfunction

β-Adrenergic Receptor Blockers

Background for Recommendations

The single most significant addition to the pharmacological management of heart failure since the publication of previous guidelines involves the use of β-receptor antagonists. This represents a noteworthy departure from traditional doctrine in which β-blocking agents were classified as contraindicated in the setting of left ventricular systolic dysfunction. A solid foundation of both clinical and experimental evidence now firmly supports their use in heart failure with the aim of reducing both morbidity and mortality (16,22,23).

β-Blocker therapy for heart failure has been advocated by some investigators since the 1970s (24). During the subsequent 2 decades, many small- to medium-sized placebo-controlled trials, which used a variety of agents, showed several common findings: 1) the use of β-blockers in mild to moderate heart failure was generally safe when initiated at low doses and gradually up-titrated under close observation; 2) improvement in left ventricular ejection fraction was observed in all trials that lasted at least 3 months; and 3) there was wide variability in the effects of β-blockade on exercise tolerance but improvement in outcome and symptomatic benefits was noted in many studies. These generally positive findings stimulated additional, large-scale clinical trials that have provided an impressive body of evidence that supports the use of β-blockers in patients with heart failure caused by left ventricular systolic dysfunction. The recommendations that follow are derived from nearly 2 decades of research that include basic science data, animal models, and clinical trial experience in over 10,000 patients (25,26).

Although this is a major advance in efficacy, identification of appropriate candidates for β-blocker therapy is essential to ensure safe and effective treatment. Prescribing physicians should understand the potential risks of β-blocker therapy, as well as the benefits. The interested practitioner who is unfamiliar with β-blocker initiation and titration may first seek further education and counsel from sources such as the Heart Failure Society of America or local and regional heart failure specialty centers.

> **Recommendation 1.** β-blocker therapy should be routinely administered to clinically stable patients with left ventricular systolic dysfunction (left ventricular ejection fraction less than or equal to 40%) and mild to moderate heart failure symptoms (ie, NYHA class II–III, Appendix A) who are on standard therapy, which typically includes ACE inhibitors, diuretics as needed to control fluid retention, and digoxin (Strength of Evidence = A).

The most persuasive outcome in heart failure management remains all-cause mortality. Combined endpoints, including mortality or hospitalization and mortality or hospitalization for heart failure, have also emerged as key outcomes. These latter endpoints reflect a more

comprehensive assessment of the influence of therapy on quality of life and disease progression and are assuming more importance as mortality rates decline with treatment advances. The substantial beneficial effect of β-blocker therapy on these endpoints has been well shown in clinical trials of symptomatic patients (NYHA class II–III) treated with carvedilol, bisoprolol, or metoprolol controlled release/extended release (CR/XL)(27–29). Trials with these agents encompass the combined, worldwide experience with β-blocker therapy in patients with chronic heart failure who were stable on background therapy, including ACE inhibitors (over 90%) and diuretics (over 90%). Digoxin was common as background therapy, particularly in studies conducted in the United States. Trial results indicate that both selective and nonselective β-blockers, with and without ancillary properties, have significant efficacy in heart failure. β-Blocking agents with intrinsic sympathomimetic activity appear to have a negative impact on survival and should not be used in heart failure patients.

Metoprolol. The MDC Study was an early trial that included 383 patients with heart failure caused by nonischemic causes, NYHA class II–III symptoms, and a left ventricular ejection fraction of less than or equal to 40% (30). Patients with coronary artery disease were excluded. Study results showed a 34% reduction in risk in patients treated with metoprolol, although this strong trend toward benefit ($P = .058$) was entirely attributable to a reduction in the frequency of cardiac transplantation listing in the treatment group. In fact, the absolute number of deaths in the metoprolol group was higher than in the placebo group (23 v 19, $P = .69$).

The MERIT-HF Trial evaluated the effect of metoprolol CR/XL with all-cause mortality as the primary endpoint. The trial included 3,991 patients with NYHA class II–IV heart failure, although 96% of the study patients were functional class II or III (31). In this study, investigators were allowed to select the starting dose of metoprolol CR/XL. Seventy-nine percent chose 25 mg as the starting dose for class II patients, and 77% chose 12.5 mg for class III–IV patients. The target dose was 200 mg and doses were up-titrated over a period of 8 weeks. Premature discontinuation of blinded therapy occurred in 13.9% of those treated with metoprolol CR/XL and 15.3% of those in the placebo group ($P = .90$). The study results revealed a 34% reduction in mortality in the metoprolol group (relative risk of .66; 95% confidence interval [CI], .53 to .81; $P = .0062$ after adjustment for interim analyses), with annual mortality rates of 11% in the placebo and 7.2% in the metoprolol CR/XL group (29).

Bisoprolol. The CIBIS Study evaluated the effects of bisoprolol in 641 patients with left ventricular systolic dysfunction caused by ischemic or nonischemic causes

and NYHA class III–IV heart failure (32). The primary endpoint was all-cause mortality, and hospitalization for worsening heart failure was one of the secondary outcomes of interest. The initial bisoprolol dose was 1.25 mg/day, which was increased to a maximum dose of 5 mg/day. The trial found no significant reduction in all-cause mortality in patients treated with bisoprolol (20% reduction bisoprolol v placebo, $P = .22$) (32). The risk of hospitalization was significantly reduced by 34% (28% placebo group v 19% bisoprolol group, $P < .01$).

The favorable trends seen in CIBIS led to the larger CIBIS II Study, which ultimately was prematurely terminated as a result of a significant reduction in mortality in the bisoprolol arm (28). These results were obtained from 2,647 patients who were followed for an average of 1.3 years. Over 80% of the patients were judged to be NYHA class III at enrollment. Background therapy included ACE inhibitors in 96% and diuretic in 99% of the study patients, whereas 52% were taking digoxin. In contrast to the original CIBIS Study, CIBIS II had a similar starting dose of 1.25 mg but had a greater target dose of 10 mg daily of bisoprolol. More stringent criteria for defining ischemic cardiomyopathy were used. Treatment with bisoprolol reduced the annual mortality rate by 34% (13.2% placebo v 8.8% bisoprolol; hazard ratio .66; 95% CI, .54 to .81; $P < .0001$). Hospitalizations for worsening heart failure were also decreased by 32% (18% placebo v 12% bisoprolol, hazard ratio .64; 95% CI, .53 to .79; $P < .0001$). Although a post hoc analysis of the CIBIS Study had suggested benefit might be consigned to patients without coronary disease, the survival benefit, with significant reductions apparent in both ischemic or nonischemic patients, was not influenced by disease origins.

Carvedilol. Carvedilol, a nonselective β-blocker and α-blocker, has been extensively investigated for treatment of heart failure caused by left ventricular systolic dysfunction. In the United States carvedilol trials, 4 separate study populations were examined and the data from 1,094 patients were combined to evaluate the effect of carvedilol therapy on the clinical progression of heart failure (27). Clinical progression was defined as worsening heart failure leading to death, hospitalization, or, in one study, a sustained increase in background medications. Patients with a left ventricular ejection fraction of 35% or less and NYHA class II–IV were eligible if they tolerated 6.25 mg of carvedilol twice per day for a 2-week, open-label, run-in period. Although this run-in phase biased the ultimately randomized patient population, less than 8% of eligible patients failed the open-label challenge. Target dosages for the studies were 50 to 100 mg/day of carvedilol that were administered in divided doses twice daily. Patients completing the run-in period were randomized based on results from their

6-minute walk test into mild, moderate, or severe trials. These studies were prematurely terminated (median follow-up, 6.5 months) by the Trial Data and Safety Monitoring Board because of reduced mortality across the 4 combined trials of patients treated with carvedilol.

Data from these combined trials indicated a substantial benefit from carvedilol treatment. The risk of mortality was 65% lower (7.8% placebo v 3.2% carvedilol; 95% CI, 39% to 80%; $P < .001$), and the combined risk of hospitalization or death was reduced by 38% (20% on placebo v 14% on carvedilol; 95% CI, 18% to 53%; $P < .001$). A significant mortality reduction was also noted when deaths that occurred in the run-in period were included in the analysis. The statistical validity of the survival analysis across the trials has been questioned because mortality was not the primary endpoint, and only 1 of the 4 trials achieved a significant result when analyzed based on the primary endpoint. Nevertheless, the magnitude of the survival benefit and the reduction in hospitalization were impressive. The survival benefit was not influenced by the cause of disease, age, gender, or baseline ejection fraction. Overall, 7.8% of the placebo group and 5.7% of the carvedilol group discontinued study medication. Data from the individual trials, PRE-CISE and MOCHA, which evaluated patients with moderate to severe heart failure, found that carvedilol reduced the risk of the combined endpoint of mortality or heart failure hospitalization by 39% to 49% (33,34). The MOCHA Study provided strong evidence for increased benefit from higher dosages (25 mg twice per day) versus lower dosages (6.25 mg twice per day) of carvedilol, so up-titration of carvedilol dosages to 25 mg twice per day is generally recommended. However, favorable effects were noted at 6.25 mg twice per day, so intolerance of high doses should not be a reason for discontinuation of therapy.

The Australia-New Zealand Carvedilol Trial enrolled 415 patients with ischemic cardiomyopathy and a left ventricular ejection fraction of less than 45% (35). Although patients with NYHA functional classes I–III were eligible, the majority enrolled were NYHA functional class 1 (30%) or II (54%). ACE inhibitors were used in 86% of the participants, whereas 76% were on diuretic therapy, and 38% were on digoxin. This trial also had a run-in phase during which 6% of the patients discontinued β-blocker therapy. During an average follow-up of 19 months, carvedilol decreased the combined risk of all-cause mortality or any hospitalization by 26% (relative risk .74; 95% CI, .57 to .95; $P = .02$). Overall mortality was 12.5% in the placebo group and 9.6% in the carvedilol group which was not statistically significant (relative risk .76; 95% CI, .42 to 1.36; $P > .10$).

Unreported or Ongoing Trials. Studies that are underway will provide additional data concerning specific aspects of the efficacy of β-blocker therapy in heart failure. The effect of bucindolol on mortality and morbidity in patients with moderate to severe heart failure has been evaluated in the BEST Study. This study enrolled a substantial number of women so the potential influence of gender on the efficacy of β-blocker therapy can be investigated. The trial has been stopped, and no results are available for analysis.

The COPERNICUS Trial is designed to assess the effect of carvedilol treatment on disease progression and survival in patients with advanced heart failure with symptoms at rest or on minimal exertion. The COMET protocol is a 3,000 patient study that directly compares the survival benefit of carvedilol versus metoprolol. This trial will provide important data concerning the relative efficacy of a selective β-blocker versus a nonselective β-blocker with ancillary properties.

Recommendation 2. β-blocker therapy should be considered for patients with left ventricular systolic dysfunction (left ventricular ejection fraction less than or equal to 40%) who are asymptomatic (ie, NYHA class I) and on standard therapy, including ACE inhibitors (Strength of Evidence = C).

Data from the SOLVD Prevention Trial prospectively illustrated the efficacy of ACE inhibitors in delaying the onset of heart failure symptoms and the need for treatment or hospitalization for heart failure in asymptomatic patients with a left ventricular ejection fraction less than or equal to 35% (36). Similar controlled, clinical trial data that support the use of a β-blocker in this clinical circumstance are not available. However, significant support for the use of β-blocker therapy in patients with asymptomatic left ventricular dysfunction can be derived from clinical trials in coronary artery disease and hypertension. Previous data indicate that β-blocker therapy should be used in patients after myocardial infarction (MI) and in patients with myocardial revascularization who have good symptomatic and functional recovery but residual ventricular systolic dysfunction. Trials in hypertension indicate that β-blocker therapy decreases the risk of developing heart failure. Given the potential of β-blockers to retard disease progression and improve ventricular function, the risk to benefit ratio seems sufficiently low to support β-blocker use in asymptomatic patients with left ventricular dysfunction, especially when the dysfunction is marked, and coronary artery disease is present.

Recommendation 3. To maximize patient safety, a period of clinical stability on standard therapy should occur before β-blocker therapy is instituted. Initiation of β-blocker therapy in patients

with heart failure requires a careful baseline evaluation of clinical status (Strength of Evidence = B).

Initiation of β-blocker therapy has the potential to worsen heart failure signs and symptoms. This risk increases with the underlying severity of the heart failure that is present. To minimize the likelihood of worsening failure, a period of treatment with standard therapy and evidence of clinical stability without acute decompensation or fluid overload is recommended before initiation of β-blocker therapy. The majority of the large-scale, β-blocker heart failure trials required that chronic heart failure be present 3 months or more before initiation of β-blocker therapy. Patients enrolled in these trials were typically treated with ACE inhibitors (if tolerated), diuretic, and digoxin for at least 2 months and were observed to be clinically stable for 2 to 3 weeks before beginning β-blocker therapy. Thus, many heart failure clinicians favor a minimum of 2 to 4 weeks of clinical stability on standard therapy before β-blocker therapy is instituted. Likewise, most clinicians discourage the initiation of β-blocker therapy in the hospital setting after treatment for new or decompensated heart failure (with or without associated inotrope administration). Some experienced clinicians initiate β-blocker therapy in the hospital in selected patients who have responded well to inpatient treatment and who can be followed closely after discharge.

Recommendation 4. There is insufficient evidence to recommend the use of β-blocker therapy for inpatients or outpatients with symptoms of heart failure at rest (ie, NYHA class IV) (Strength of Evidence = C).

β-Blocker therapy cannot be routinely recommended for NYHA class IV patients because there are currently no clinical trial data to indicate favorable long-term efficacy and safety of β-blocker therapy in this patient population. A substantial body of observational data indicates that successful institution of β-blocker therapy in patients with this degree of heart failure is problematic. If used, these agents may precipitate deterioration, and patients so treated should be monitored by a physician who has expertise in heart failure.

The number of patients with class IV heart failure at the time of β-blocker initiation in controlled clinical trials is small. Available trials, which report data on patients with severe heart failure mostly labeled as NYHA class III, show the potential problems of β-blocker therapy in this part of the heart failure spectrum. This experience is reflected in a 14-week study that evaluated the effects of β-blocker therapy in 56 patients (51 NYHA class III and 5 NYHA class IV at random-

ization) with severe left ventricular dysfunction (average left ventricular ejection fraction of 16% ± 1% and left ventricular filling pressure of 24 mm Hg ± 1 mm Hg) (37). These patients had significant impairment of exercise capacity (mean $\dot{V}o_2$ max of 13.6 mL/kg/min ± 0.6 mL/kg/min) despite ACE-inhibitor, digoxin, and diuretic therapy. Patients were believed to be clinically stable (requiring no medication adjustments) for a 2-week period before an open-label challenge was conducted. Seven patients (12%) failed to complete the open-label, run-in period, during which 5 died and 2 had nonfatal adverse reactions. Clinical parameters did not distinguish these patients from those who were able to continue in the trial. Eighteen of the 49 patients (37%) completing the run-in period experienced worsened dyspnea or fluid retention during this phase. Also, 22% experienced dizziness and required medication adjustment, which delayed up-titration during the run-in. Subsequently, an additional 12% of the patients randomized to carvedilol withdrew from the blinded arm of the study. One of the United States carvedilol trials studied patients with severe left ventricular dysfunction who had markedly reduced exercise capacity as assessed by the 6-minute walk test (38). In this trial, 131 patients with a mean left ventricular ejection fraction of 22% and severe impairment in quality of life underwent a 2-week, open-label challenge phase of 6.25 mg of carvedilol twice per day. Ten of these 131 patients (8%) were unable to complete this run-in phase, most because of worsening heart failure, dyspnea, or dizziness. Subsequently, 11% of the patients randomized to carvedilol withdrew, as did a similar number of patients (11%) in the placebo group. In the recently completed large-scale BEST Trial, the mortality trend in NYHA class III-IV patients favored the β-blocker bucindolol, but the difference from placebo was not significant. Further analysis of these preliminary findings is necessary, but the data suggest that the striking benefit of β-blockers in mild-to-moderate heart failure may not be extrapolated to those with severe symptoms.

Recommendation 5. β-Blocker therapy should be initiated at low doses and up-titrated slowly, generally no sooner than at 2-week intervals. Clinical reevaluation should occur at each titration point and with worsening of patient symptoms. Patients who develop worsening heart failure or other side effects after drug initiation or during titration require adjustment of concomitant medications. These patients may also require a reduction in β-blocker dose and, in some cases, temporary or permanent withdrawal of this therapy (Strength of Evidence = B).

β-Blocker therapy should be initiated at doses substantially less than target doses. Clinical trials required

patient reassessment at up-titration of each dose. This careful evaluation by trained nurses and/or heart failure specialists likely contributed to the relatively low withdrawal rates and safety profiles observed in the clinical trials.

Treatment for symptomatic deterioration may be required during β-blocker titration, but with appropriate adjustments in therapy, most patients can be maintained and generally achieve target doses. There is a risk of worsening heart failure, and vasodilatory side effects may occur with certain agents. Worsening heart failure is typically reflected by increasing fatigue, lower exercise tolerance, and weight gain. Increased diuretic doses may be required for signs and symptoms of worsened fluid retention. Treatment options also include temporary down-titration of the β-blocker to the last tolerated dose. Abrupt withdrawal should be avoided. A minimum period of stability of 2 weeks should occur before further up-titration is attempted. Hypotensive side effects may often resolve with reduction in diuretic dose. Temporary reductions in ACE inhibitor dose may be helpful for symptomatic hypotension not obviated by staggering the schedule of vasoactive medications. Administration of carvedilol with food may alleviate vasodilatory side effects as well.

If β-blocker treatment is interrupted for a period exceeding 72 hours and the patient is still judged a candidate for this therapy, drug treatment should be reinitiated at 50% of the previous dose. Subsequent up-titration should be conducted as previously described.

Recommendation 6. In general, patients who experience a deterioration in clinical status or symptomatic exacerbation of heart failure during chronic maintenance treatment should be continued on β-blocker therapy (Strength of Evidence = C).

Clinical decompensation that occurs during stable maintenance therapy is less likely caused by chronic β-blocker therapy than other factors (diet or medication noncompliance, ischemia, arrhythmia, comorbid disease, infection, or disease progression). In these situations, maintaining the current β-blocker dose while relieving or compensating for the precipitating factor(s) is most often the best course. Data from patients randomized to continue or discontinue β-blocker therapy in this setting are not currently available. However, studies of the withdrawal of β-blocker therapy in patients with persistent left ventricular systolic dysfunction but improved and stable clinical heart failure have revealed a substantial risk of worsening heart failure and early death after discontinuation of β-blocker therapy (39,40).

Recommendation 7. Patient education regarding early recognition of symptom exacerbation and side effects is considered important. If clinical uncertainty exists, consultation with clinicians who have expertise in heart failure and/or specialized programs with experience in β-blocker use in patients with heart failure is recommended (Strength of Evidence = B).

In certain patients, frequent return visits for dose-titration may be difficult to accommodate in a busy clinical practice. Trained personnel, including nurse practitioners, physicians' assistants, and pharmacists with physician supervision, may more efficiently perform patient education and reevaluation during up-titration. Heart failure specialty programs are more likely to have the resources to provide this follow-up and education (41). Consultation or referral may be particularly beneficial when the clinical heart failure status of the patient is uncertain or problems arise during initiation of therapy or dose-titration that may cause unwarranted discontinuation of therapy. Ideal patients for β-blocker therapy should be compliant and have a good understanding of their disease and their overall treatment plan. Patients should be aware that symptomatic deterioration is possible early in therapy and that symptomatic improvement may be delayed for weeks to months.

Unresolved Therapeutic Issues

Combining β-Blocking Agents With Amiodarone Therapy. Concomitant use of amiodarone was generally precluded in the trials evaluating carvedilol and most other β-blockers. However, the use of this agent for rate control of atrial arrhythmia or for maintenance of sinus rhythm is common in heart failure patients. Drug interactions between β-blockers and amiodarone are possible, including symptomatic bradycardia, and may limit the maximum tolerated dose of the β-blocker. When the combination is used, the smallest effective dose of amiodarone should be employed. Given the lack of a clear survival benefit, amiodarone is not a substitute for β-blocker therapy in heart failure patients who are candidates for this therapy.

Implantation of Cardiac Pacemakers. Given the strength of evidence that supports β-blocker therapy in patients with symptomatic heart failure, some physicians would consider pacemaker implantation when symptomatic bradycardia or heart block occur during the initiation of this therapy, although no data are available to support such use. Consideration should be given, after weighing risks and benefits, to the withdrawal of other drugs that may have bradycardia effects.

Duration of Therapy. Whether patients experiencing marked improvement in left ventricular systolic dysfunction and heart failure symptoms during therapy can be successfully withdrawn from β-blocker therapy remains to be established. Concern continues that such patients would experience worsening after β-blocker withdrawal, either in systolic function or symptoms, over a time period that is undefined. Until clinical trial data indicate otherwise, the duration of β-blocker therapy must be considered indefinite.

Digoxin

Background for Recommendations

Although little controversy exists as to the benefit of digoxin in patients with symptomatic left ventricular systolic dysfunction and concomitant atrial fibrillation, the debate continues over its current role in similar patients with normal sinus rhythm. Recent information regarding digoxin's mechanism of action and new analyses of clinical data from the DIG Trial and the combined PROVED and RADIANCE Trial databases provide additional evidence of favorable efficacy that was unavailable to previous guideline committees (42–47). In fact, this information has recently formed the basis of Food and Drug Administration (FDA) approval of digoxin for the treatment of mild to moderate heart failure (48). Digoxin, a drug that is inexpensive and can be given once daily, represents the only orally effective drug with positive inotropic effects approved for the management of heart failure. The committee's consensus is that digoxin, when used in combination with other standard therapy, will continue to play an important role in the symptomatic management of the majority of patients with heart failure.

The efficacy of digoxin for the treatment of heart failure caused by systolic dysfunction has traditionally been attributed to its relatively weak positive inotropic action that comes from inhibition of sodium-potassium adenosine triphosphatase (ATPase) that results in an increase in cardiac myocyte intracellular calcium. However, in addition to positive inotropy, digitalis has important, neurohormonal-modulating effects in patients with chronic heart failure, including a sympathoinhibitory effect that cannot be ascribed to its inotropic action (49,50). Digoxin also ameliorates autonomic dysfunction as evidenced by studies of heart rate variability, which indicates increased parasympathetic and baroreceptor sensitivity during therapy (51).

Recommendation 1. Digoxin should be considered for patients who have symptoms of heart failure (NYHA class II–III, Strength of Evidence = A and NYHA class IV, Strength of Evidence = C) caused by left ventricular systolic dysfunction while receiving standard therapy.

Digoxin increases left ventricular ejection fraction and alleviates symptomatic heart failure as evidenced by drug-related improvement in exercise capacity and reductions in heart-failure-associated hospitalization and emergency room visits. Digoxin should be used in conjunction with other forms of standard heart failure therapy including ACE inhibitors, diuretics, and β-blockers.

The DIG Trial, a randomized, double-blind, placebo-controlled trial in over 7,000 patients with heart failure, showed a neutral effect on the primary study endpoint and mortality from any cause during an average follow-up of approximately 3 years (42). In the main trial, 6,800 patients with left ventricular ejection fraction less than or equal to 45% were randomized to digoxin or placebo, in addition to diuretics and ACE inhibitors. A total of 1,181 deaths occurred on digoxin (34.8%) and 1,194 on placebo (35.1%) for a risk ratio of .99 (95% CI, .91 to 1.07; P = .80). These results differ from other oral agents with inotropic properties that have been associated with an adverse effect on mortality. In addition, the need for hospitalization and cointervention (defined as increasing the dose of diuretics and ACE inhibitors or adding new therapies for worsening heart failure) was significantly lower in the digoxin group, even in those patients who were not previously taking digoxin. Fewer patients on digoxin compared with placebo were hospitalized for worsening heart failure (26.8% v 34.7%; risk ratio .72; 95% CI, .66 to .79; P < .001). These long-term data are consistent with recent results obtained from an analysis of the combined PROVED and RADIANCE databases (45). In this analysis, patients who continued digoxin as part of triple therapy with diuretics and an ACE inhibitor were much less likely to develop worsening heart failure (4.7%) than those treated with a diuretic alone (39%, P < .001), diuretic plus digoxin (19%, P = .009), or diuretic plus an ACE inhibitor (25%, P = .001).

Although there are no clinical trial data (level A evidence) for the efficacy of digoxin in patients with NYHA class IV heart failure, there is evidence that digoxin works across the spectrum of left ventricular systolic dysfunction. A prespecified subgroup analysis of patients enrolled in the DIG Trial with evidence of severe heart failure (as manifested by left ventricular ejection fraction less than 25%, or cardiothoracic ratio [CTR] greater than .55) showed the benefit of digoxin (48). The following reductions in the combined endpoint of all-cause mortality or hospitalization were seen on digoxin compared with placebo: 16% reduction (95% CI, 7% to 24%) in patients with a left ventricular ejection fraction of less than 25%, and a 15% reduction (95% CI, 6% to 23%) in patients with a CTR of greater than .55 (43). Reductions

in the risk of the combined endpoint of heart failure-related mortality or hospitalization were even more striking: 39% (95% CI, 29% to 47%) for patients with left ventricular ejection fraction less than 25%, and 35% (95% CI, 25% to 43%) for patients with a CTR greater than .55 (48).

Evidence for the efficacy of digoxin in patients with mild symptoms of heart failure has been provided by a recent retrospective, cohort analysis of the combined PROVED and RADIANCE data (52). The outcome of patients in these trials who were randomized to digoxin withdrawal or continuation was categorized by using a prospectively obtained heart failure score based on clinical signs and symptoms. Patients in the mild heart failure group (heart failure score of 2 or less) who were randomized to have digoxin withdrawn were at increased risk of treatment failure and had deterioration of exercise capacity and left ventricular ejection fraction compared with patients who continued digoxin (all $P < .01$). Patients in the moderate heart failure group who had digoxin withdrawn were significantly more likely to experience treatment failure than either patients in the mild heart failure group or patients who continued digoxin (both $P < .05$). These data suggest that patients with left ventricular systolic dysfunction benefit from digoxin despite only mild clinical evidence of heart failure.

In summary, a large body of evidence supports the efficacy of digoxin in patients with symptomatic heart failure caused by left ventricular systolic dysfunction. Digoxin has been shown to decrease hospitalizations, as well as emergency room visits; decrease the need for co-intervention; and improve exercise capacity (42–44,53,54). Taken as a whole, these clinical trial data provide support for digoxin's beneficial effect on morbidity and neutral effect on mortality (42).

Recommendation 2. In the majority of patients, the dosage of digoxin should be .125 mg to .25 mg daily (Strength of Evidence = C).

Recent data suggest that the target dose of digoxin therapy should be lower than traditionally assumed. Although higher doses may be necessary for maximal hemodynamic effects (55), beneficial neurohormonal and functional effects appear to be achieved at relatively low serum digoxin concentrations (SDC) typically associated with daily doses of .125 mg to .25 mg of digoxin (55–57). The utility of lower SDC is supported by recent clinical trial data: the mean SDC achieved in the RADIANCE Trial was 1.2 ng/mL and in the DIG Trial was 0.8 ng/mL (42,44). Recent retrospective, cohort analysis of the combined PROVED and RADIANCE databases indicates that patients with a low SDC (less than .9 ng/mL) were no more likely to experience worsening symptoms of heart failure on maintenance digoxin than those with

a moderate (.9 to 1.2 ng/mL) or high (greater than 1.2 ng/mL) SDC (41). All SDC groups were significantly less likely to deteriorate during follow-up compared with patients withdrawn from digoxin.

Therefore, patients with left ventricular systolic dysfunction and normal sinus rhythm should be started on a maintenance dosage of digoxin (no loading dose) of .125 or .25 mg once daily based on ideal body weight, age, and renal function. For patients with normal renal function, a dosage of digoxin of .25 mg/day will be typical. Many patients with heart failure have reduced renal function and should begin on .125 mg daily. In addition, patients with a baseline conduction abnormality, or who are small in stature or elderly, should be started at .125 mg/day, which can be up-titrated if necessary. Once dosing has continued for a sufficient period for serum concentration to reach steady state (typically in 2 to 3 weeks), some clinicians consider the measurement of a SDC, especially in elderly patients or those with impaired renal function in which the digoxin dose is often not predictive of SDC. SDC measurements may be considered when 1) a significant change in renal function occurs; 2) a potentially interacting drug (amiodarone, quinidine, or verapamil) is added or discontinued; or 3) confirmation of suspected digoxin toxicity is necessary in a patient with signs or symptoms and/or electrocardiographic changes consistent with this diagnosis. Samples for trough SDC should be drawn more than 6 hours after dosing. Otherwise, the result is difficult to interpret because the drug may not be fully distributed into tissues.

Recommendation 3. In patients with heart failure and atrial fibrillation with a rapid ventricular response, the administration of high doses of digoxin (greater than .25 mg) for the purpose of rate control is not recommended. When necessary, additional rate control should be achieved by the addition of β-blocker therapy or amiodarone (Strength of Evidence = C).

Digoxin continues to be the drug of choice for patients with heart failure and atrial fibrillation. However, the traditional practice of arbitrarily increasing the dose (and SDC) of digoxin until ventricular response is controlled should be abandoned because the risk of digoxin toxicity increases as well. Digoxin alone is often inadequate to control ventricular response in patients with atrial fibrillation, and the SDC should not be used to guide dosing to achieve rate control. Therefore, digoxin should be dosed in the same manner as in a patient with heart failure and normal sinus rhythm.

Digoxin slows ventricular response to atrial fibrillation through enhancement of vagal tone. However, with exertion or other increases in sympathetic activity, vagal tone may decrease and ventricular rate accelerate. Addi-

tion of a β-blocker or amiodarone 1) complements the pharmacological action of digoxin and provides more optimal rate control; 2) allows the beneficial clinical effects of digoxin to be maintained; and 3) limits the risk of toxicity that may occur if digoxin is dosed to achieve a high SDC (58). For patients who have a contraindication to β-blockers, amiodarone is a reasonable alternative. If amiodarone is added, the dose of digoxin should be reduced, and the SDC should be monitored so that the serum concentration can be maintained in the desired range. Some clinicians advocate the short-term, intravenous administration of diltiazem for the acute treatment of patients with very rapid ventricular response, especially those with hemodynamic compromise. This drug is not indicated for long-term management because its negative inotropic effects may worsen heart failure.

Unresolved Therapeutic Issues

Combination With β-Blockers. β-Blocker therapy has become pivotal in the management of heart failure. However, the majority of patients enrolled in controlled clinical trials that study the efficacy of digoxin were not taking β-blockers. Therefore, it is uncertain whether or not digoxin should be routinely included as part of a β-blocker regimen for symptomatic heart failure caused by left ventricular systolic dysfunction. There are attractive features of combining digoxin with β-blocker therapy in the treatment of heart failure. The majority of heart failure patients have coronary artery disease and may be at risk for transient episodes of myocardial ischemia that could cause catecholamine release and sudden cardiac death. Combining digoxin with a β-blocker may preserve the beneficial effects of digoxin on the symptoms of heart failure while minimizing the potential detrimental effects of this therapy on catecholamine release in the setting of ischemia (47).

Combination With Diuretics. Non–potassium-sparing diuretics can produce electrolyte abnormalities such as hypokalemia and hypomagnesemia, which increases the risk of digoxin toxicity. The combination of digoxin with a potassium-sparing diuretic would be a potentially safer alternative. Further study will be necessary to carefully elucidate the efficacy and safety of combining digoxin with these agents.

Anticoagulation and Antiplatelet Drugs

Background for Recommendations

Patients with heart failure are recognized to be at increased risk for thromboembolic events that can be arterial or venous in origin. In addition to atrial fibrilla-

tion and poor ventricular function (which promote stasis and increase the risk of thrombus formation), patients with heart failure have other manifestations of hypercoagulability. Evidence of heightened platelet activation: increased plasma and blood viscosity; and increased plasma levels of fibrinopeptide A, β-thromboglobulin, D-dimer, and von Willebrand factor (59–61) have been found in many patients. Despite a predisposition, estimates regarding the incidence of thromboemboli in patients with heart failure vary substantially between 1.4 and 42 per 100 patient years (62–65). Although variability in the reported incidence likely results from differences in the populations studied and the methods used to identify these events, the consensus is that pulmonary and systemic emboli are not common in heart failure patients. Traditionally, the issue of anticoagulation in patients with heart failure centered on warfarin. Growing recognition of the importance of ischemic heart disease as a cause of heart failure suggests that the role of antiplatelet therapy must be considered in patients with this syndrome as well.

Previous guidelines have recommended warfarin anticoagulation in patients with heart failure complicated by atrial fibrillation and in heart failure patients with prior thromboembolic events (18,19). Warfarin anticoagulation specifically was not recommended in patients with heart failure in the absence of these indications. There have been no randomized, controlled trials of warfarin in patients with heart failure. Therefore, recommendations regarding its use, in the absence of atrial fibrillation or clinically overt systemic or pulmonary thromboemboli, must be made on the basis of cohort data and expert opinion. The likely incidence of thromboembolic events and the possibility of averting them with warfarin are important considerations for any guideline recommendation. In addition, the potential beneficial effects of warfarin on coronary thrombotic events, independent of embolic phenomenon, must be taken into account. The substantial clinical trial data that reflect the beneficial effects of antiplatelet therapy in patients with ischemic heart disease suggest that new guideline recommendations for heart failure should address the role of this form of therapy in patients with left ventricular dysfunction.

Anticoagulation

Recommendation 1. All patients with heart failure and atrial fibrillation should be treated with warfarin (goal, international normalized ratio (INR) 2.0 to 3.0) unless contraindicated (Strength of Evidence = A).

The committee agrees with previous guideline recommendations that concern warfarin therapy in patients with heart failure complicated by atrial fibrillation. The

benefit of warfarin anticoagulation in this setting is well established through several randomized trials (66). Patients with heart failure commonly have atrial fibrillation. Warfarin anticoagulation should be implemented in all of these patients unless clear contraindications exist.

Recommendation 2. Warfarin anticoagulation merits consideration for patients with left ventricular ejection fraction of 35% or less. Careful assessment of the risks and benefits of anticoagulation should be undertaken in individual patients (Strength of Evidence = B).

Cohort analyses examining the relationship between warfarin use and noncoronary thromboembolism in patients with heart failure have not consistently yielded positive findings (62,63,65,67–69). It is possible that the lack of consistent benefit was related to the low incidence of identifiable embolic events in these populations. However, these studies do not make a convincing argument for the use of warfarin to prevent embolic events in the absence of atrial fibrillation or a previous thromboembolic episode.

In contrast, a recent cohort analysis of the SOLVD population focused on the relation between warfarin use and the risk of all-cause mortality rather than risk for embolic events (70). After adjustment for baseline differences, patients treated with warfarin at baseline had a significantly lower risk of mortality during follow-up (adjusted hazard ratio .76; 95% Cl, .65 to .89; P = .0006). In addition to a mortality benefit, warfarin use was also associated with a significant reduction in the combined endpoint of death or hospitalization for heart failure (adjusted hazard ratio .82; 95% CI, .72 to .93; P = .002). In the SOLVD population, the benefit associated with warfarin use was not significantly influenced by 1) presence or absence of symptoms (treatment trial v prevention trial), 2) randomization to enalapril or placebo, 3) gender, 4) presence or absence of atrial fibrillation, 5) age, 6) ejection fraction, 7) NYHA class, or 8) origins of disease.

The benefit associated with warfarin use in the cohort analysis of the SOLVD population was related to a reduction in cardiac mortality. Specifically, there was a significant reduction among warfarin users in deaths that were identified as sudden, in deaths associated with heart failure, and in fatal MI. In contrast (yet in agreement with previous cohort analyses), there was no significant difference in deaths considered cardiovascular but noncardiac, including pulmonary embolism and fatal stroke. Some caution is needed in consideration of this finding because the number of cardiovascular deaths that were noncardiac was far less than the number of cardiac deaths.

Reduction in ischemic events is one potential explanation for the apparent benefit from warfarin in the

SOLVD Study. Warfarin users showed a reduced rate of hospitalization for unstable angina or nonfatal MI. Prior investigations of patients after acute MI showed that warfarin anticoagulation, when started within 4 weeks, reduces the incidence of fatal and nonfatal coronary events, as well as pulmonary embolus and stroke (71).

As with other post hoc, cohort analyses, it is possible that the findings from the SOLVD Study may result from differences between the treatment groups that were not identified and for which statistical correction could not adequately adjust. For this reason, evidence from any cohort study must be considered less powerful compared with evidence derived from randomized, controlled trials. Nevertheless, in the absence of randomized data, the SOLVD cohort analysis represents reasonable evidence to support more aggressive use of warfarin anticoagulation than previously recommended in patients with reduced left ventricular ejection fraction and sinus rhythm. The data from this analysis provide no information regarding the ideal warfarin dose in this patient population. Therefore, the dosing recommendation should likely conform to that derived from previous randomized trials performed in patients without mechanical prosthetic valves (INR 2.0 to 3.0).

Antiplatelet Drugs

Recommendation 1. With regard to the concomitant use of ACE inhibitors and acetylsalicylic acid (ASA), each medication should be considered on its own merit for individual patients. Currently, there is insufficient evidence concerning the potential negative therapeutic interaction between ASA and ACE inhibitors to warrant withholding either of these medications in which an indication exists (Strength of Evidence = C).

Strong evidence supports the clinical benefit of aspirin in ischemic heart disease and atherosclerosis (72–75). However, recent post hoc analyses of large randomized trials involving ACE inhibitors in heart failure and post-MI suggest the possibility of an adverse drug interaction between ASA and ACE inhibitors (76–78). A retrospective cohort analysis of the SOLVD Study found that patients on antiplatelet therapy (assumed to be ASA in the great majority of patients) derived no additional survival benefit from the addition of enalapril. Data from CONSENSUS II and GUSTO-1 in post-MI patients, suggest not only no additive benefit, but the possibility of a negative effect on mortality from the combination of ASA and ACE inhibition. In contrast, an unadjusted, retrospective registry study in patients with chronic coronary artery disease did not support an adverse interaction (79). Interestingly, in an adjusted analysis of the subset of patients with heart failure in this study, the

beneficial effects of aspirin seemed less evident in patients taking ACE inhibitors. Despite these provocative post hoc findings, no prospective studies have yet been reported that concern the possible adverse interaction between ACE inhibitors and aspirin. To date, there is no clear evidence of harm from the combination of ASA and ACE inhibitors in patients with heart failure (76).

There is also some evidence that the potential interaction between ASA and ACE inhibitors may be dose related. A recent meta-analysis of all hypertension and heart failure patients who have received both ASA and ACE inhibitors suggests that ASA at doses equal to or less than 100 mg showed no interaction with ACE inhibitors (80). Any interaction, if observed, occurred at higher doses of aspirin.

A potential mechanism for the hypothesized adverse interaction between ASA and ACE inhibitors in patients with heart failure involves prostaglandin synthesis. ACE inhibition is believed to augment bradykinin which, in turn, stimulates the synthesis of various prostaglandins that may contribute vasodilatory and other salutary effects. In the presence of ASA, the bradykinin-induced increase in prostaglandins should be attenuated or blocked, which potentially reduces the benefits of ACE inhibition. Invasive hemodynamic monitoring has shown that the acute hemodynamic effect of enalapril is blunted by concomitant administration of aspirin (81). Another possibility is that ASA and ACE inhibitors act in a similar fashion in heart failure, therefore no added benefit is gained from the combination. ACE inhibitors appear to reduce ischemic events in heart failure patients possibly through antithrombotic effects, which could mimic those of antiplatelet agents. Recent study results that suggest ASA may have independent beneficial action on ventricular remodeling support the hypothesis of similar mechanisms of action for ACE inhibitors and ASA (82).

Development of the adenosine diphosphate (ADP) antagonists, ticlopidine and clopidogrel, provides alternative therapy for platelet inhibition that does not appear to influence prostaglandin synthesis (83). In direct comparison with aspirin, large-scale clinical trial results have established the efficacy of clopidogrel in the prevention of vascular events in patients with arteriosclerotic disease (84). Clinical data are limited with ADP antagonists in heart failure. However, hemodynamic evaluation found a similar reduction in systemic vascular resistance in heart failure patients treated with the combination of ACE inhibitors and ticlopidine versus ACE inhibitors alone, which suggests no adverse hemodynamic interaction with ACE inhibition with this type of antiplatelet compound (85). Definitive resolution of the therapeutic implications of the ASA/ACE inhibitor interaction and the appropriate alternative therapy, if any, in heart failure awaits the results of additional clinical research studies.

Angiotensin II Receptor Blockers

Background for Recommendations

Angiotensin II (AT) receptor blockers (ARBs) differ in their mechanism of action compared with ACE inhibitors. Rather than inhibiting the production of AT by blockade of ACE, ARBs block the cell surface receptor for AT. ARBs that are currently available are selective and only effectively inhibit the AT_1 subtype of this receptor. Theoretical benefits of ARBs include receptor blockade of AT produced by enzymes other than ACE and maintenance of ambient AT to maintain or increase stimulation of AT_2 receptors. AT_1 receptor antagonism is important because this receptor appears to mediate the classical adverse effects associated with AT in heart failure. In contrast, the AT_2 receptor subtype appears to counterbalance AT_1 receptor stimulation by causing vasodilation and inhibiting proliferative and hypertrophic responses (86). Thus, the selective receptor blockade of the current ARBs may be particularly advantageous. Theoretical concerns about ARB therapy include the potential deleterious effects of increased AT levels and AT_2 receptor–mediated enhancement of apoptosis. Whether ARBs have beneficial effects similar to ACE inhibitors on the course of coronary artery disease remains to be determined. ARBs may or may not influence bradykinin concentrations, which are anticipated to rise with ACE inhibitor therapy and may contribute to their efficacy.

The hemodynamic actions of ARBs have, thus far, been similar to ACE inhibitors for reduction of blood pressure in hypertension and lowering of systemic vascular resistance in heart failure (87). ARBs have a similar mild-to-modest effect on exercise capacity and produce a comparable reduction in norepinephrine relative to ACE inhibitors (88).

Recommendation 1. ACE inhibitors rather than ARBs continue to be the agents of choice for blockade of the renin-angiotensin system in heart failure, and they remain the cornerstone of standard therapy for patients with left ventricular systolic dysfunction with or without symptomatic heart failure (Strength of Evidence = A).

At present, it is not possible to predict where ARBs will ultimately reside among accepted therapies for heart failure. Although the initial small ELITE Trial suggested a greater benefit from a losartan dosage of 50 mg daily than from a captopril dosage of 50 mg 3 times daily on mortality in elderly patients with heart failure (89), the ELITE II Mortality Trial, which included more than 3,000 patients (90), showed no comparative benefit from losartan and a trend for a better outcome and fewer sudden deaths with captopril (91). This result provides no evidence that the low dose (50 mg) of losartan that

was tested is better than an ACE inhibitor for treating heart failure, but it does not exclude the efficacy of a higher dose designed to provide continuous inhibition of the AT_1 receptor. Tolerability of losartan was better than of captopril, primarily because of an ACE-inhibitor cough. But the well-established efficacy of the ACE inhibitors on outcome in the post-MI period, in diabetes, in atherosclerosis, and in heart failure mandates that this drug group remains agents of choice for inhibiting the renin-angiotensin system in heart failure. The RE-SOLVD Trial suggested no major differences in efficacy of candesartan and enalapril, with a trend favoring enalapril during the study period of 43 weeks (92). The OPTIMAAL and VALIANT Studies will provide information specifically about the role of ARBs versus ACE inhibitors in the post-MI population.

Currently, ACE inhibitors continue to be regarded as the therapy of choice to inhibit the renin-angiotensin system in patients with asymptomatic and symptomatic left ventricular dysfunction. There is no current rationale to recommend initiating ARBs in patients with new onset heart failure or for switching from a tolerated ACE-inhibitor regimen to an ARB in patients with chronic heart failure.

Recommendation 2. All efforts should be made to achieve ACE inhibitor use in patients with heart failure caused by left ventricular dysfunction. Patients who are truly intolerant to ACE inhibitors should be considered for treatment with the combination of hydralazine and isosorbide dinitrate (Hyd-ISDN) (Strength of Evidence = B) or an ARB (Strength of Evidence = C).

Previous large-scale trials do not specifically address the role of ARB and Hyd-ISDN in patients who are intolerant to ACE inhibitors. One arm of the CHARM Study has been specifically designed to test the effectiveness of candesartan in patients with systolic dysfunction who are intolerant to ACE inhibitors. The primary endpoint in this study will be a composite of cardiovascular death and the time until first hospitalization for heart failure. For now, ARBs offer a reasonable alternative in the heart failure or post-MI patient who is truly intolerant to ACE inhibition. Intolerance because of cough should always trigger a careful reevaluation for congestion. If congestion is present, cough should abate with increases of diuretic that should allow ACE-inhibitor use to continue (93). It should be emphasized that patients intolerant to ACE inhibitor because of renal dysfunction, hyperkalemia, or hypotension are often intolerant to ARBs as well. ACE inhibitor intolerance because of persistent symptomatic hypotension in advanced heart failure may represent severe dependence on the hemodynamic support of the renin-angiotensin system, which generally would predict hypotension with ARB use as well.

The combination of Hyd-ISDN has not been studied in the post-MI population, but sufficient experience exists to support its use in the ACE-inhibitor–intolerant patient with symptomatic heart failure. Hydralazine blocks the development of nitrate tolerance, which argues for the use of combination therapy. Although they were not studied alone in a heart failure mortality trial, oral nitrates represent another reasonable alternative for patients who are intolerant to both ACE inhibitors and hydralazine.

Unresolved Therapeutic Issues

Combination Therapy With ACE Inhibitors and ARBs. Interest has grown in the potential utility of combining ACE inhibitors and ARBs in patients with heart failure. Initial data suggest that the combination yields more vasodilation and decreased blood pressure than either agent alone. The addition of losartan to an ACE inhibitor has been found to improve exercise capacity compared with an ACE inhibitor alone (94). Preliminary data from the RESOLVD Trial suggest that ventricular dilation and neuroendocrine activation may be best reduced with combination therapy, but other endpoints were not clearly affected. Trials are currently underway to determine the safety, as well as benefit, of more complete blockade of the renin-angiotensin system. The Val-HeFT Trial is a large-scale investigation of the effect of valsartan in addition to ACE inhibitors on morbidity and mortality in symptomatic patients with heart failure caused by systolic dysfunction. One arm of the CHARM Study will also examine the effect of the addition of candesartan in patients with symptomatic, systolic dysfunction treated with an ACE inhibitor. Preliminary data from the RESOLVD Trial suggest that combination therapy may be even more efficacious when used in conjunction with β-blocker treatment. Results from Val-HeFT and CHARM in the subset of patients treated with β-blocker therapy will provide more information concerning this strategy.

Combination therapy represents a rational option when treating severe hypertension or other vasoconstriction but cannot, at present, be recommended as routine therapy in the absence of a proven superiority to ACE-inhibitor therapy alone.

Antiarrhythmic Drug and Device Therapy

Background for Recommendations

Ventricular arrhythmias are common in heart failure patients, and sudden cardiac death continues to account

for a significant proportion of the mortality in this syndrome. In the setting of heart failure, sudden death may arise from a variety of causes including bradyarrhythmias, conduction disturbances, electromechanical dissociation, acute MI, or pulmonary embolus. However, the majority of these deaths are thought to be caused by ventricular tachyarrhythmias. Therefore, there has been considerable interest in the potential role of antiarrhythmic therapy in heart failure patients.

Antiarrhythmic drugs, particularly Vaughn Williams class Ia (quinidine and procainamide) and Ic (flecainide and encainide) agents, have been shown to suppress ventricular ectopy and nonsustained ventricular tachycardia in heart failure patients. However, these agents have also been shown to substantially increase the risk of serious arrhythmia and premature death in other cardiovascular diseases (95,96). Class III agents also reduce the frequency of serious ventricular arrhythmia in heart failure, but it is uncertain if this action is important for reducing the risk of sudden death. It is also evident that patients with heart failure are at higher risk for proarrhythmic effects of these agents. This has been identified with class Ia (quinidine, procainamide), class Ic, and class III (dofetilide) agents. Furthermore, virtually all antiarrhythmic agents have been shown to have adverse hemodynamic effects. Therefore, evidence for a favorable risk to benefit ratio is essential before antiarrhythmic therapy can be recommended as prophylactic therapy for heart failure patients.

Class III drugs (amiodarone; D-sotalol; D,I-sotalol; and dofetilide) have recently been more thoroughly evaluated. Early results with 2 class III agents (amiodarone and D,L-sotalol) appeared to offer more promise, perhaps because of their β-blocking effects. However, results with pure class III agents (D-sotalol, dofetilide) have not shown benefit. In the SWORD Trial, D-sotalol produced a significant increase in total and cardiac mortality rates in post-MI patients (97). In the preliminary reporting of the DIAMOND-CHF Trial, dofetilide had no effect on all-cause mortality (98).

Although results with D-sotalol and dofetilide have not been encouraging, interest has remained strong in the potential role of amiodarone, another class III agent, for reducing sudden death in patients with heart failure and left ventricular systolic dysfunction. At the same time, there is growing experience with implantable cardiac defibrillators (ICDs) in patients with symptomatic and asymptomatic arrhythmias. Many of these patients have symptomatic systolic dysfunction, which has raised the issue of the appropriate role of this therapeutic intervention in patients with heart failure.

Recommendation 1. Based on the inconclusive results of clinical trials with amiodarone and its known toxicity, this drug is not recommended

for the primary prevention of death in patients with chronic heart failure (Strength of Evidence = A).

The GESICA Trial, which was conducted in 26 hospitals in Argentina, randomized 516 predominantly male patients, with an average age of 59 years, to standard therapy with or without the open-label (not placebo-controlled) addition of amiodarone (99). Seventy-nine percent of the patients were NYHA class III or IV; their mean left ventricular ejection fraction was 20%, and the majority (61%) were thought to have heart failure of nonischemic origins. The trial was prematurely discontinued when a 28% reduction (95% CI, 4% to 45%; $P = .024$) in all-cause mortality, the primary endpoint, was observed. Comparable reductions in deaths classified as either sudden (27%) or caused by progressive heart failure (23%) were seen. Post hoc analyses suggested that the primary benefit was in patients with higher pretreatment heart rates (greater than 90 bpm).

A second trial of amiodarone in heart failure patients was CHF-STAT, a Veterans Affairs Co-Operative Study conducted in the United States (100). This randomized, double-blind, placebo-controlled study enrolled 674 patients with a mean age of 66 years. The majority (56%) had NYHA class II symptoms, and their mean ejection fraction was 26%. At least 71% were known to have ischemic cardiomyopathy. In contrast to the GESICA Study, there were no differences in all-cause or cardiac mortality or sudden death rates between the amiodarone and placebo groups. The overall survival at 2 years was 69% (95% CI, 64% to 74%) in the amiodarone group and 71% (95% CI, 66% to 76%) in the placebo group ($P = .60$). There was a trend toward improved survival with amiodarone in patients classified as having nonischemic cardiomyopathy ($P = .07$). In this subgroup, there was a 44% decrease in the post hoc endpoint of cardiac death or hospitalization (95% CI, 13% to 64%; $P = .01$). Importantly, patients with baseline ventricular arrhythmias (asymptomatic, nonsustained ventricular tachycardia) did not manifest any benefit, even though amiodarone therapy was effective in suppressing these arrhythmias. Amiodarone treatment produced a significant increase in left ventricular ejection fraction but no clinical evidence of improvement in heart failure.

Several important differences between the GESICA and CHF-STAT patient populations are apparent. The GESICA population included younger patients, women, a higher proportion of nonischemic cardiomyopathy, and more severe heart failure (evidenced by a more advanced NYHA class, lower ejection fractions, and higher mortality rates). Far fewer patients in the GESICA population (4.6% v 27%) discontinued amiodarone therapy. It is uncertain whether 1 or more of these factors, the lack of

blinding, or the play of chance is responsible for the differing outcomes of these 2 trials.

Although they did not strictly involve heart failure patients, 2 recent post-MI trials that use amiodarone are also relevant for this guideline. EMIAT randomized 1,486 European patients with ejection fractions less than 40% (without entry arrhythmia criteria) after acute myocardial infarction (101). No differences in all-cause or cardiac mortality were observed, but a strong trend toward a reduction in death classified as arrhythmic in origin or resuscitated ventricular fibrillation was present (risk reduction 35%; 95% CI, 0% to 58%; $P = .05$). Concomitant β-blocker was used in 44% of the study patients. Post hoc, subgroup analysis found a more favorable odds ratio with the combination of amiodarone and β-blocker (relative risk .48; 95% CI, .20 to 1.01) than with amiodarone and no β-blocker (relative risk 1.15; 95% CI, .80 to 1.65; $P = .06$ for the interaction). The CAMIAT Trial, conducted in Canada, randomized 1,202 post-MI patients who had greater than 10 premature ventricular contractions per hour or at least one 3 beat run of nonsustained ventricular tachycardia (102). There was no ejection fraction criteria for inclusion in the trial. Again, amiodarone did not show a favorable effect on all-cause mortality (18% reduction; 95% CI, 16% to 43%; $P = .129$) or cardiac mortality (22% reduction; 95% CI, 16 to 48%; $P = 0.108$). However, the combination of arrhythmic death and resuscitated ventricular fibrillation was significantly decreased ($P = .016$). β-blocker was used in 59% of the study patients, and post hoc analysis found that these patients had an 87% reduction of all cardiovascular events compared with patients on amiodarone and no β-blocker ($P < .008$).

Finally, a meta-analysis of 13 amiodarone trials (8 post-MI, 5 congestive heart failure [CHF]), that was published in 1997 revealed a decrease in total mortality with amiodarone therapy, but the finding was of marginal statistical significance (relative risk on amiodarone therapy of .87; 95% CI, .78 to .99; $P = .03$) (103). This analysis showed a substantial decrease in antiarrhythmic/sudden death rate (relative risk .71; 95% CI, .59 to .85; $P = .0003$). Subgroup analysis showed no difference in the degree of benefit from amiodarone between post-MI patients and chronic congestive heart failure patients.

Thus, the clinical trial experience with amiodarone in post-MI patients and heart failure patients remains equivocal. It is not known to what degree the benefits, if any, of amiodarone are related to its β-blocking activity. However, given the known toxicity of amiodarone and the evidence of reduction in mortality and morbidity with β-blockers, we recommend that amiodarone not be used as a substitute for β-blockers in patients with heart failure.

Recommendation 2. Based on evidence from a number of clinical trials that included patients with heart failure and reduced ejection fractions, it is recommended that patients with heart failure who have been resuscitated from primary ventricular fibrillation or who have experienced hemodynamically destabilizing sustained ventricular tachycardia be treated with ICDs (Strength of Evidence = B).

No clinical trials of ICD therapy, specifically in heart failure patients, have yet been completed. However, in several major studies of these devices, a majority of patients had systolic dysfunction, and a substantial number had clinical heart failure. These trials (MADIT, AVID, CIDS, and CASH) consistently indicate that survival of patients with life-threatening arrhythmias is improved with ICD placement compared with antiarrhythmic therapy (104–106). Thus, in otherwise suitable patients with symptomatic heart failure (based on overall prognosis and functional status), ICD should be considered as first-line therapy for these arrhythmias. Additional data are required before this approach can be recommended for patients with NYHA class IV symptoms. In a setting in which patients have progressed to end-stage symptoms, ICDs have the potential to prolong survival when quality of life is unsatisfactory. To date, there are no data to support the use of ICDs in heart failure patients with asymptomatic ventricular arrhythmias, although 3 important trials (SCD-HeFT, MADIT II, and DEFINITE) are addressing this question (107,108).

Recommendation 3. Amiodarone is the preferred drug when antiarrhythmic therapy is indicated in patients with heart failure for supraventricular tachycardia not controlled by digoxin or β-blocker or for patients with life-threatening ventricular arrhythmia who are not candidates for ICD placement (Strength of Evidence = B).

Antiarrhythmic drugs may be indicated for the management of supraventricular arrhythmias and for the treatment of symptomatic ventricular arrhythmias in heart failure patients who are not candidates for device therapy. Amiodarone should be considered the agent of choice for these indications based on the clear evidence of the safety of this agent in patients with heart failure, low incidence of proarrhythmic effects in general, and identified risk of proarrhythmia and hemodynamic deterioration with alternative antiarrhythmic agents.

Aldosterone Antagonists

Background for Recommendations

Sustained activation of aldosterone appears to play an important role in the pathophysiology of heart failure (109,110). Increased renin and AT levels contribute to the stimulation of aldosterone secretion in heart failure. Elevated circulating levels of this hormone enhance sodium retention and potassium and magnesium loss in heart failure. Aldosterone upsets autonomic balance by increasing sympathetic activation and parasympathetic inhibition and promotes cardiac and vascular structural remodeling through collagen synthesis (111–113).

Although ACE inhibition may transiently decrease aldosterone secretion, there are diverse stimuli other than AT for the production of this hormone (114). Studies suggest a rapid return of aldosterone to levels similar to those before ACE inhibition (115). Aldosterone-receptor blockers have not been frequently used in patients with heart failure because of concerns about side effects and hyperkalemia in the presence of ACE inhibitors. However, the potential pathophysiological role of aldosterone and a pilot study that suggested low doses of spironolactone seemed to be tolerated in heart failure patients, led to additional investigation of this drug in patients with severe heart failure (116).

> **Recommendation 1. Administration of the aldosterone antagonist spironolactone at low dose (ie, 12.5 mg to 25 mg once daily) should be considered for patients receiving standard therapy who have severe heart failure (with recent or current NYHA class IV) caused by left ventricular systolic dysfunction. Patients treated in this manner should have a normal serum potassium level (less than 5.0 mmol/L) and adequate renal function (creatinine less than 2.5 mg/dL) (Strength of Evidence = A). Serum potassium concentration should be monitored after the first week and at regular intervals thereafter and after any change in dose of spironolactone or in the dose of concomitant medications that may affect potassium balance. Consideration should be given to lowering or eliminating supplemental potassium (Strength of Evidence = A).**

The RALES Trial was designed to determine the effect of a low dose of spironolactone on survival in severely symptomatic (with recent or current NYHA class IV) heart failure patients treated with an ACE inhibitor, loop diuretic, and, in many cases, digoxin (117). The study enrolled a total of 1,663 patients with severe left ventricular systolic dysfunction (ejection frac-

tion of 35% or less) from ischemic and nonischemic causes, and all-cause mortality was the prespecified primary endpoint. There were 386 deaths in the placebo group (46%) compared with 284 (35%) in the spironolactone group (relative risk of death .70; 95% CI, .60 to .82; $P < .001$). The risk of death from progressive heart failure or sudden death was reduced. The frequency of hospitalization for heart failure was 35% lower in patients treated with spironolactone compared with placebo (relative risk of hospitalization .65; 95% CI, .54 to .77; $P < .001$). Greater improvement was noted in NYHA functional class during follow-up for those receiving spironolactone. However, deaths in class III patients were designated as worsened class. Therefore, this functional improvement likely reflects the mortality benefit of the drug.

The inclusion and exclusion criteria for the RALES Trial are important to consider when applying the study results to clinical practice. Testifying to the goal of studying patients with advanced heart failure, the yearly mortality rate in the placebo group was high, particularly relative to other recent heart failure mortality studies. The potential benefit of aldosterone antagonists in patients with milder heart failure and lower risk cannot be determined from the present data. Patients with potassium levels greater than 5.0 mmol/L were excluded, as well as patients with abnormal renal function (defined as a creatinine greater than 2.5 mg/dL). Patients recruited into the trial met the potassium inclusion criteria despite the frequent concomitant use of potassium supplementation at baseline (28%). These patient characteristics may be necessary to avoid excessive hyperkalemia during spironolactone treatment. It should be noted that only 10% of placebo and 11% of spironolactone patients in the RALES Trial were treated with β-blocker therapy.

Spironolactone should be used in conjunction with other standard therapy, including ACE inhibitors, digoxin, diuretics, and β-blockers. Spironolactone should be initiated at a dosage of 12.5 mg to 25 mg per day. The mean dosage at the end of the RALES Study in the spironolactone group was 26 mg per day, which suggests that up-titration to the maximum target dosage of 50 mg per day was infrequent. Serum potassium and creatinine should be closely monitored in the first few weeks of therapy. If the serum potassium level increases above 5.0 mmol/L, then the dosage of spironolactone should be decreased to 25 mg every other day, along with adjustment of other medications that could contribute to hyperkalemia. In addition to hyperkalemia, gynecomastia or breast pain may be important side effects and were reported in 10% of the men randomized to spironolactone versus 1% of the men in the placebo group in the RALES Trial.

Myocarditis: Current Treatment

Background for Recommendations

Myocarditis is a distinct clinical entity with a wide variety of cardiac manifestations, including heart failure. Potential causes may include toxins, medications, physical agents, and, most importantly, infections. The most common forms appear to be postviral in origin. The pathophysiology of myocarditis has been well established in animal models with myocardial damage not only caused by direct infection, but also consequent to postinfectious, autoimmune-mediated myocardial inflammatory damage. In humans, ongoing myocardial inflammation may result in dilated cardiomyopathy, restrictive cardiomyopathy, or acute left ventricular failure without dilatation (fulminant myocarditis).

Myocarditis is histologically characterized by an active inflammatory cellular infiltrate within the myocardium and associated myocyte necrosis (the Dallas pathological criteria) (118). Although many clinicians and pathologists consider the Dallas criteria too restrictive, they have established uniform histological criteria for diagnosis and have substantially reduced the wide variation in reported rates of this disease. Although the inflammatory infiltrate is lymphocytic in over 90% of patients, eosinophilia or giant cell formation may occasionally be seen as well. The clinical features of myocarditis are extremely varied and range from asymptomatic electrocardiographic abnormalities (observed during viral Coxsackie B outbreaks in the community) to severe dilated cardiomyopathy with fulminant congestive heart failure leading to transplantation or death (119). Myocarditis may also cause ventricular arrhythmias, heart block, or mimic acute myocardial infarction (120,121). Both acute and chronic dilated cardiomyopathies may result from inflammatory heart disease. The histological differentiation of myocarditis from idiopathic dilated cardiomyopathy remains controversial because several published series suggest no difference in long-term prognosis, regardless of the presence or absence of myocardial inflammation (122). Nonetheless, many clinicians believe that myocarditis is a potentially reversible form of cardiomyopathy and continue to perform endomyocardial biopsy in search of its presence. It is clear that clinical signs and symptoms of classic Coxsackie B myocarditis are not sufficiently sensitive to unequivocally establish the correct diagnosis. Fever, elevation in serum creatine kinase or troponin, an earlier viral illness, or pericarditis are present in fewer than 30% of cases of classic Coxsackie-mediated disease (119). Furthermore, Coxsackie titers are elevated in over 40% of patients with dilated cardiomyopathy.

Controversy continues to surround the best approach to the management of patients who are considered to have myocarditis. The following recommendation is based on a review of currently available data from uncontrolled and controlled evaluation of immunomodulatory therapy for the treatment of myocarditis.

> **Recommendation 1. An evidence-based approach to treatment suggests that an effective therapy for myocarditis remains to be identified. Routine use of immunosuppressive therapies cannot be recommended for patients with myocarditis (Strength of Evidence = B).**

Uncontrolled Studies

Over 20 uncontrolled trials have been reported during the past 15 years on the use of immunosuppressive agents in the treatment of biopsy-proven lymphocytic myocarditis (118). Therapies have included prednisone alone, prednisone and azathioprine, prednisone and cyclosporine, and short courses of OKT3. Virtually all immunosuppressive protocols can result in rapid histological improvement or resolution of the inflammatory component of the disease. Unfortunately, little or no correlation exists between histological improvement and ventriculographic improvement. Improvement in ventricular function (defined as an ejection fraction rise greater than 10 ejection fraction units) has been reported to range from 0% to 100% in these series (123). On average, 64% of treated patients have shown improvement in global left ventricular systolic function. However, several small clinical series have also reported a 48% rate of spontaneous improvement in ventricular function in biopsy-proven myocarditis (118,123). In addition, some investigators believe that immunosuppressive therapy may be more effective in treating "borderline" myocarditis than unequivocal active myocarditis (124). Spontaneous variation in ejection fraction and improvement in acute dilated cardiomyopathy are now well-recognized features of all forms of new onset cardiomyopathy. Thus, uncontrolled series cannot answer the question as to whether the improvement in ventricular function exhibited by some patients was actually caused by treatment or resulted from spontaneous improvement in the disease itself.

Controlled Trials

Three randomized, placebo-controlled trials have been performed that examined the role of immunosuppressive therapy in the treatment of acute dilated cardiomyopathy or myocarditis. One study randomly assigned 102 patients with dilated cardiomyopathy to treatment with either prednisone (60 mg per day) or placebo for 3 months (125). Improvement was prospectively defined as an increase in ejection fraction greater than 5 ejection fraction units. Reactive patients (n = 60) were those who

showed a fibroblastic response (n = 36), lymphocytic infiltrate (n = 2) or immunoglobulin deposition (n = 16) on endomyocardial biopsy, a positive gallium cardiac scan (n = 7), or an elevated sedimentation rate (n = 18). Nonreactive patients (n = 42) had none of these features. At 3 months, 67% of the reactive patients treated with prednisone had an improvement in ejection fraction compared with only 28% of the reactive control patients (P = .004). Nonreactive patients did not improve significantly with prednisone. However, the mean change in ejection fraction in the prednisone-treated groups was only from 18% to 22%. Nonreactive patients showed no change in ejection fraction (17% to 19%). After 3 months, reactive patients treated with prednisone were switched to alternate-day therapy. However, after 6 months, the earlier improvement in ejection fraction was no longer present. The trial concluded that prednisone had marginal clinical benefit and should not be administered as standard therapy for dilated cardiomyopathy patients. A major criticism of this trial was only a small number of patients had histologically verified myocarditis.

The experience of 52 patients with recently diagnosed idiopathic dilated cardiomyopathy who were treated with either conventional therapy alone or in combination with prednisone has been reported (126). An inflammatory response on an endomyocardial biopsy specimen was present in 23% of the overall population, 13% of whom had Dallas criteria myocarditis. Immunosuppressed patients received 50 mg of prednisone daily for 2 weeks, followed by a taper by 10 mg every 2 weeks until the drug was discontinued. Biopsy-documented myocarditis resolved in all patients within 3 months, regardless of treatment modality. Survival at 24 months was the primary endpoint of the study. Prednisone-treated patients had a 24-month survival rate of 64% ± 12% compared to 83% ± 8% for the untreated patients (P = .57). The presence of myocardial inflammation did not influence survival. Thus, prednisone was determined to be ineffective in improving the primary endpoint in the study.

Results of the MTT Study, which examined immunosuppressive therapy that consisted of prednisone and cyclosporine, have been published (127). A total of 111 patients with histologically verified myocarditis and a left ventricular ejection fraction less than 45% were randomized to receive conventional therapy alone or combined with immunosuppression for 6 months. The primary outcome measure was prespecified as change in ejection fraction at 28 weeks. The majority of patients received prednisone and cyclosporine immunosuppressive treatment as the azathioprine treatment limb was prematurely terminated because of slow study enroll-

ment. For the group as a whole, the left ventricular ejection fraction improved from 25% at baseline to 34% at 28 weeks. The mean change in ejection fraction did not differ between treatment groups. A higher left ventricular ejection fraction at baseline or shorter duration of symptoms, but not the randomized treatment assigned, were positive independent predictors of improvement in ejection fraction at 28 weeks. There was no difference in survival between treatment groups; the mortality rate for the entire group was 20% at 1 year and 56% at 4.8 years. This study is the only sizable randomized trial specifically focused on treatment of patients with myocarditis. Unfortunately, prednisone and cyclosporine-based immunosuppressive therapy produced no clinical benefit.

High-dose immune globulin has been shown to be effective treatment for a variety of immunologically mediated diseases such as Kawasaki's disease. The use of intravenous immune globulin (2 g/kg) in 21 consecutive children treated for presumed acute myocarditis has been described (128). Response to therapy was compared with 25 historical control patients who did not receive intravenous immune globulin. Sixty-two percent of treated patients had biopsy-proven myocarditis compared with 40% of historical controls in this series. Treated patients were more likely to achieve normal left ventricular function during the first year after presentation. At 12 months, the probability of survival trended towards improvement in intravenous immune globulin–treated patients (84% v 60%, P = ns). No adverse effects of this treatment were reported.

The use of intravenous immune globulin in 10 adult patients with dilated cardiomyopathy (only one of whom had biopsy-proven myocarditis) has been reported (129). All patients had NYHA class III or IV heart failure symptoms and a left ventricular ejection fraction below 40%. One patient died, while the remaining 9 patients were discharged; ejection fraction in the survivors increased from 24% to 41%. An ongoing, multicenter, randomized trial of immune globulin therapy has recently completed enrollment and results will be available later in 1999.

In summary, although anecdotal case reports and uncontrolled small series have suggested a benefit of immunosuppressive therapy, controlled studies have shown no clinical benefit as judged by improvement in either ejection fraction or survival. Immunomodulatory therapy rather than immunosuppression may ultimately prove beneficial for patients with acute dilated cardiomyopathy caused by inflammatory heart disease, but its efficacy requires validation by the ongoing, randomized clinical treatment trial.

Appendix A

Criteria for NYHA Functional Classification for Chronic Heart Failure Patients' Functional Capacity (130)

Class 1 No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.

Class 2 Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class 3 Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class 4 Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix B

Glossary of Clinical Trials

AVID	Antiarrhythmics Versus Implantable Defibrillators
BEST	Beta-blocker Evaluation of Survival Trial
CAMIAT	Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
CAPRIE	Clopidogrel Vs Aspirin in Patients at Risk of Ischemic Events
CASH	Cardiac Arrest Study Hamburg
CHF–STAT	Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy
CHARM	Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity
CIBIS	Cardiac Insufficiency Bisoprolol Study
COMET	Carvedilol or Metoprolol European Trial
CONSENSUS	Cooperative North Scandinavian Enalapril Survival Study
CONSENSUS II	Cooperative New Scandinavian Enalapril Survival Study II
COPERNICUS	Carvedilol Prospective Randomized Cumulative Survival Trial
CIBIS II	Cardiac Insufficiency Bisoprolol Study II
DEFINITE	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation
DIAMOND	Danish Investigation of Arrhythmia and Mortality on Dofetilide
DIG	Digitalis Investigation Group
ELITE	Evaluation of Losartan In The Elderly
ELITE II	Losartan Heart Failure Survival Study—ELITE II
EMIAT	European Myocardial Infarction Amiodarone Trial
GESICA	Grupo de Estudio de Sobrevida en Insuficiencia Cardiaca en Argentina
GUSTO 1	Global Utilization of Streptokinase and TPA for Occluded coronary arteries
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MADITII	Multicenter Automatic Defibrillator Implantation Trial II
MDC	Metoprolol in Dilated Cardiomyopathy trial
MERIT-HF	Metoprolol CR/XL Randomized Intervention Trial in Heart Failure
MOCHA	Multicenter Oral Carvedilol in Heart-failure Assessment
MTT	Myocarditis Treatment Trial
OPTIMALL	Optimal Therapy in Myocardial Infarction with the Angiotensin II Antagonist Losartan
PRECISE	Prospective Randomized Evaluation of Carvedilol In Symptoms and Exercise
PROVED	Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin
RADIANCE	Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme
RALES	Randomized Aldactone Evaluation Study
RESOLVD	Randomized Evaluation of Strategies for Left Ventricular Dysfunction
SAVE	Survival And Ventricular Enlargement
SCD-HeFT	Sudden Cardiac Death in Heart Failure: Trial of Prophylactic Amiodarone Versus Implantable Defibrillator Therapy
SOLVD	Studies Of Left Ventricular Dysfunction
SWORD	Survival With Oral D-sotalol
Val-HeFT	Valsartan Heart Failure Trial
VALIANT	Valsartan in Acute Myocardial Infarction

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